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Customer No.: 07278
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Docket No: 2094/1E286-US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

in re Application of: Jeffrey M. LINNEN; Kevin M. GORMAN

Serial No.: 09/493,353 Art Unit: 1655

Filed: January 28, 2000 Examiner: J. Goldberg

For: OLIGONUCLEOTIDE PRIMERS FOR EFFICIENT DETECTION OF HEPATITIS C VIRUS (HCV) AND METHODS OF USE THEREOF

RESPONSE TO OFFICIAL ACTION AND AMENDMENT UNDER 37 C.F.R. § 1.116

Hon. Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

In response to the Office Action dated October 22, 200, and in accordance with Rule 116 of the Rules of Practice, please enter the following amendments and consider the accompanying remarks. The amendments are made pursuant to the requirements of Rule 121 in the Rules of Practice. Applicants submit concurrently herewith: (1) a copy of the amended claims (attached hereto

at Exhibit Tab A) marked up, as required under 37 C.F.R. § 121(c)(ii), to show all changes relative to the previous version of each claim; (2) a true copy of a Declaration by Kevin M. Gorman Under 37 C.F.R. § 1.132 (the "Gorman Declaration"), including Exhibit 1; (3) a Petition for Extension of Time, accompanied by the appropriate fee and requesting that the time period for responding to the Office Action be extended for **three** months (*i.e.* from **January 22, 2002** up to and including **Monday, April 22, 2002**); and (4) a Notice of Appeal accompanied by the appropriate fee.

It is believed that no other fees are required for these submissions. However, should the U.S. Patent and Trademark Office determine that any additional fee is due or that a refund is owed for this application, the Commissioner is authorized and requested to charge any fee(s) due and/or credit any refund(s) owed to Deposit Account No. 04-0100.

Please amend the application as follows:

IN THE CLAIMS:

Amend claims 1, 9 , 27, 35, 40, 41, 43 and 54, as indicated in the accompanying Exhibit A, so that the claims read as follows:

1. (Twice Amended) A method for detecting the presence of Hepatitis C Virus (HCV) RNA in a biological sample, said method comprising:

(A) performing a reverse transcription reaction using, as a template, RNA derived from said sample to produce HCV-specific reverse transcription products;

(B) amplifying said reverse-transcription products using one or more pairs of oligonucleotide primers specific for HCV to produce HCV-specific amplification products,

wherein said pairs are selected from the group consisting of:

(a) forward primer 5'-CAGAAAGCGTCTAGCCATGGCGTTAGTA-3' (C69F28) <SEQ ID NO. 1> and reverse primer 5'-CGGTTCCGCAGAGACCACTATGGCTCTC-3' (C133R26) <SEQ ID NO. 4>; and

(b) forward primer 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 2> and reverse primer 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 7>; and

(C) detecting said amplification products, wherein detection of said amplification products indicates the presence of HCV RNA in said sample.

9. (Twice Amended) A method for amplifying Hepatitis C Virus (HCV) DNA, which method comprises performing a polymerase chain reaction on a DNA sample containing HCV DNA using one or more pairs of oligonucleotide primers specific for HCV to produce HCV-specific amplification products, wherein said pairs are selected from the group consisting of:

(a) forward primer 5'-CAGAAAGCGTCTAGCCATGGCGTTAGTA-3' (C69F28) <SEQ ID NO. 1> and reverse primer 5'-CGGTTCCGCAGACCACTATGGCTCTC-3' (C133R26) <SEQ ID NO. 4>; and

(b) forward primer 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 2> and reverse primer 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 7>.

27. (Twice Amended) A method for detecting the presence of Hepatitis C Virus (HCV) RNA in a biological sample, said method comprising:

(A) performing a reverse transcription reaction using as a template RNA derived from said sample to produce HCV-specific reverse transcription products;

(B) amplifying said reverse-transcription products using one or more pairs of 5' NCR oligonucleotide primers specific for HCV and one or more pairs of

3' NCR oligonucleotide primers to produce HCV-specific amplification products,

wherein said 5' NCR primer pairs are selected from the group consisting of:

(a) forward primer 5'-CAGAAAGCGTCTAGCCATGGCGTTAGTA-3' (C69F28) <SEQ ID NO. 1> and reverse primer 5'-CGGTTCCGCAGACCACTATGGCTCTC-3' (C133R26) <SEQ ID NO. 4>; and

(b) forward primer 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 2> and reverse primer 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 7>; and

wherein each of said pairs of 3' NCR oligonucleotide primers comprises a forward primer consisting of the oligonucleotide 5'-GGTGGCTCCATCTTAGCCCTAGTCACG-3' (1F27) <SEQ ID NO. 8> and a reverse primer consisting of the oligonucleotide 5'-AGGCCAGTATCAGCACTCTCTGCAGTC-[3] 3' (57R27) <SEQ ID NO. 9>; and

(C) detecting said amplification products, wherein detection of said amplification products indicates the presence of HCV RNA in said sample.

35. (Twice Amended) A method for amplifying Hepatitis C Virus (HCV) DNA, which method comprises performing a polymerase chain reaction on a DNA sample containing HCV DNA using one or more pairs of 5' NCR oligonucleotide primers specific for HCV and one or more pairs of 3' NCR oligonucleotide primers to produce HCV-specific amplification products, wherein said 5' NCR primer pairs are selected from the group consisting of:

(a) forward primer 5'-CAGAAAGCGTCTAGCCATGGCGTTAGTA-3' (C69F28) <SEQ ID NO. 1> and reverse primer 5'-CGGTTCCGCAGACCACTATGGCTCTC-3' (C133R26) <SEQ ID NO. 4>; and

(b) forward primer 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 2> and reverse primer 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 7>; and

wherein each of said pairs of 3' NCR oligonucleotide primers comprises a forward primer consisting of the oligonucleotide 5'-GGTGGCTCCATCTTAGCCCTAGTCACG-3' (1F27) <SEQ ID NO. 8> and a reverse primer consisting of the oligonucleotide 5'-AGGCCAGTATCAGCACTCTCTGCAGTC-3' (57R27) <SEQ ID NO. 9>.

40. (Twice Amended) An oligonucleotide selected from the group consisting of:

5'-CAGAAAGCGTCTAGCCATGGCGTTAGTA-3' (C69f28) <SEQ ID NO. 1>;

5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 2>;

5'-CGGTTCCGCAGACCACTATGGCTCTC-3 (C133R26) <SEQ ID NO. 4>;

5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 7>;

D5

5'-GGTGGCTCCATCTTAGCCCTAGTCACG-3' (1F27) <SEQ ID NO. 8>;

5'-AGGCCAGTATCAGCACTCTCTGCAGTC-3 (57R27) <SEQ ID NO. 9>;

5'-GGGTCCTGGAGGCTGCACGACACTCAT-3' (C96-22-PRB) <SEQ ID NO. 11>;

5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-27-PRB) <SEQ ID NO. 12>;

5'-TTTCGCGACCCAACACTACTCGGCT-3' (C252-25-PRB) <SEQ ID NO. 13>;

5'-GCGGCTCACGGACCTTTCACAGCTA-3' (30PRB25) <SEQ ID NO. 14>; and

5'-ATGCGGCTCACGGACCTTTCACAGC-3' (32PRB25) <SEQ ID NO. 15>.

41. (Twice Amended) An HCV-specific amplification primer oligonucleotide selected from the group consisting of:

5'-CAGAAAGCGTCTAGCCATGGCGTTAGTA-3' (C69F28) <SEQ ID NO. 1>;

5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 2>;

5'-CGGTTCCGCAGACCACTATGGCTCTC-3' (C133R26) <SEQ ID NO. 4>;

5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 7>;

5'-GGTGGCTCCATCTTAGCCCTAGTCACG-3' (1F27) <SEQ ID NO. 8>; and

5'-AGGCCAGTATCAGCACTCTCTGCAGTC-3' (57R27) <SEQ ID NO. 9>.

D6

43. (Amended) A kit for amplifying HCV DNA derived from HCV RNA, said kit comprising one or more pairs of 5' NCR oligonucleotide primers, wherein said 5' NCR primer pairs are selected from the group consisting of:

(a) forward primer 5'-CAGAAAGCGTCTAGCCATGGCGTTAGTA-3' (C69F28) <SEQ ID NO. 1> and reverse primer 5'-CGGTTCCGCAGACCACTATGGCTCTC-3' (C133R26) <SEQ ID NO. 4>; and

(b) forward primer 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 2> and reverse primer 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 7>.

D7

54. (Twice Amended) A kit for detecting the presence of HCV DNA, said kit comprising one or more pairs of 5' NCR oligonucleotide primers, wherein said 5' NCR primer pairs are selected from the group consisting of:

(a) forward primer 5'-CAGAAAGCGTCTAGCCATGGCGTTAGTA-3' (C69F28) <SEQ ID NO. 1> and reverse primer 5'-CGGTTCCGCAGACCACTATGGCTCTC-3' (C133R26) <SEQ ID NO. 4>; and

(b) forward primer 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 2> and reverse primer 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 7>.

REMARKS

Claims 1-64 are currently pending in this application. Claims 1, 9, 27, 35, 40, 41, 43 and 54 have been amended in this response. In particular, the Markush groups recited in each of these claims have been modified to cancel certain nucleotide sequences that were originally specified therein. Accordingly, claims 1-64 will remain pending upon entry of these amendments.

The amendments are made without admission and without prejudice to Applicants' right to pursue the canceled subject matter in either this or other (*e.g.*, related) patent application. Instead, these amendments have been made to expedite allowance of this application and to present the rejected claims in better form for consideration on appeal. No new matter has been introduced. Entry and consideration of these amendments are therefore respectfully requested.

THE REJECTIONS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

The Examiner has maintained the rejections of the pending claims as being obvious over various combinations of the following references:

(a) Han *et al.*, "Characterization of the terminal regions of hepatitis C viral RNA: Identification of conserved sequences in the 5' untranslated region and poly(A) tails at the 3' end" *Proc. Natl. Acad. Sci. U.S.A.* 1991, 88:1711-1715 ("Han");

(b) Kolykhalov *et al.*, "Identification of a Highly Conserved Sequence Element at the 3' Terminus of Hepatitis C Virus Genome RNA" *J. Virology* 1996, 70(6):3363-3371 ("Han");

(c) U.S. Patent No. 5,837,463 issued November 17, 1998 to Tanaka *et al.*, ("Tanaka");

(d) Encke *et al.*, "Total Chemical Synthesis of the 3' Untranslated Region of the Hepatitis C Virus with Long Oligodeoxynucleotides" *J. Virological Methods* 1998, 74:117-121 ("Encke");

(e) U.S. Patent No. 5,846,704 issued December 8, 1998 to Maertens *et al.* ("Maertens"); and

(f) Ahern, "Biochemical Reagent Kits Offer Scientists Good Return on Investment" *The Scientist* 1995, 9(15):20 ("Ahern").

Briefly, the Examiner argues that the references of Kiolykhalov, Tanaka and Encke teach a conserved region of the Hepatitis C Virus ("HCV") genome, referred to as the 3'-untranslated region ("3'-UTR"), and its use for genotyping HCV. The references of Han and Maertens are said to teach another conserved

region of the HCV genome, referred to as the 5'-untranslated region ("5'-UTR"). Moreover, Maertens allegedly teaches oligonucleotide primers from this region, at least some of which are said to overlap with oligonucleotide sequences recited in the pending claims. The Ahern reference discusses the utility and desirability of kits for biological assays in general, but is not related *per se* to the amplification or detection of HCV.

The Examiner has acknowledged that none of the cited references specfically teaches the particular primer sequences of this invention. However, the Examiner argues that, because the full length 5' and 3'-UTR sequences from to which those primers hybridze were known, the particular primers of this invention would have been obvious to persons of ordinary skill in the art when this application was filed. More specifically, the Examiner contends that the teaching in those references is sufficient to motivate a person skilled in the art to try using those primers to amplify and/or detect HCV (*e.g.*, in a clinical assay) and, moreover, that a skilled artisan would have had a reasonable expectation of success.

Applicants note with appreciation, however, that the Examiner has also noted data presented in this application that compares certain primers of the invention to a commercial assay that existed when the application was filed, the Roche AMPLICOR assay. The Examiner indicates in the Office Action that these data indicate unexpected results and that, accordingly, the claims would be

allowable if restricted to the particular primer sequences compared in those experiments. *See*, in particular, on page 39 of the Office Action.

While applicants respectfully submit that *all* of the oligonucleotide sequences recited in the pending claims are non-obvious over the cited prior art, the pending claims have been amended pursuant to the Examiner's suggestions to specify those primer sequences that the Examiner has indicated are allowable. Specifically, the independent claims have been amended to specifically recite primer sequences selected from: (i) C69F28 and C133R26 (SEQ ID NOS:1 and 4, respectively); and (ii) C131F25 and C294R25 (SEQ ID NOS:2 and 7, respectively). The oligonucleotide sequences C143F26 (SEQ ID NO:3), C282R27 (SEQ ID NO:5) and C287R27 (SEQ ID NO:6), to which the Examiner has objected, are no longer recited in the amended claims.

Applicants respectfully point out, however, that independent claims 27, 35, 40 and 41 recite additional primer sequences: 57R27 (SEQ ID NO:9) and 1F27 (SEQ ID NO:8). As explained below, these oligonucleotides, like the other oligonucleotide sequences of this invention, have unexpected properties and are therefore non-obvious over the cited prior art. Applicants therefore respectfully decline to cancel the recitation of these sequences in the pending claims.

To better demonstrate this point, Applicants respectfully direct the Examiner's attention to the Declaration of Kevin M. Gorman Under 37 C.F.R. § 1.132 (the "Gorman Declaration"), a true copy of which is submitted

concurrently herewith. The Gorman Declaration describes experiments in which the named inventors of this application tested various oligonucleotides derived from the 3'-UTC region of HCV to determine which particular oligonucleotide(s), if any, could successfully prime reverse transcription in clinical samples of HCV. See, in particular, ¶¶ 8-9 of the Gorman Declaration.[1]

In a set of experiments, described in ¶¶ 10-12 of the Gorman Declaration, the inventors tested one particular revers primer recited in the pending claims, 57R27 (SEQ ID NO:9), and compared its ability to reverse transcribe and amplify a clinical HCV sample with the ability of other primers (referred to in the Gorman Declaration as 67R25, 66R25 and 72R27) to reverse transcribe and amplify that same sample. All of these primers were designed to be complementary to the 3' NC region of HCV (the Gorman Declaration at ¶ 10). Yet only the primer that is part of this invention (*i.e.*, the primer 57R27), when used with the forward primer 1F27 (SEQ ID NO:8) amplified HCV in that sample with sufficient sensitivity and specificity for use in a clinical assay (the Gorman Declaration at ¶ 13). Although, the primers 66R25 and 67R25 may have reverse transcribed and/or amplified HCV nucleic acids in the clinical sample tested, they did so with poor specificity so that the amplified cDNA appeared "as broad smears on the ethidium bromide gels, and not as sharp distinct bands which are preferable,

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[1] Applicants note that both the Gorman Declaration and the instant application refer to the 3'-UTR taught by Tanaka and/or Kolykhalov as the 3' non-coding ("NC") region of the HCV genome.

e.g., for clinical applications" (the Gorman Declaration at ¶ 12). The remaining primer, 72R27, completely failed to reverse transcribe or amplify the HCV nucleic acids, so that very little or no PCR product was observed (the Gorman Declaration at ¶ 12).

In summary, the Gorman Declaration demonstrates that only certain oligonucleotides derived from the HCV 3'-UTR may successfully those nucleic acids with sufficient specificity and/or sensitivity for use in clinical and many other applications. Moreover, and as also stated in the Gorman Declaration (see, specifically, at ¶ 9), when this application was first filed it was not possible to predict *a priori* whether a particular oligonucleotide would successfully amplify HCV; *i.e.*, a skilled artisan could not have had a reasonable expectation of success. It is therefor only with the benefit of hindsight provided by the instant application that a skilled artisan can reasonably expect success. However, reliance on hindsight to arrive at a determination of obviousness is not permissible. *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention"). See also, *In re Fitch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992), citing *In re Gorman*, 933 F.2d 982, 987, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991) ("It is impermissible to use the claimed invention as an instruction manual of 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious").

For all of the foregoing reasons, Applicants submit that the obviousness rejections have been overcome and/or obviated. Applicants therefore respectfully request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

For the reasons stated above, Applicants believe that the Examiner's rejections of the pending claims have been overcome and that the claims, as amended, are in condition for allowance. Accordingly, the withdrawal of all objections and rejections, and reconsideration of the application are respectfully requested. The Examiner is invited to contact Applicants' undersigned representative at the below indicated telephone number if she believes it may advance prosecution of this application. An allowance is earnestly sought.

Respectfully submitted,

Dated: April 22, 2002

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